

Internal Bone Seeking Radionuclides and Monocyte Counts

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Abstract

Statistically significant monocyte depression is reported in four populations with internal exposure to bone-seeking radionuclides (uranium, radium, thorium, lead 210, strontium 90 and plutonium) at relatively low dose levels within current maximum permissible doses for the public. Both the proportion of the population with monocytopenia and the severity of the depression appear dose related. Secondary effects of monocytopenia are iron deficient anemia and impaired cellular immune system. The purpose of this paper is to alert others to the effect and solicit their experience and interpretation. It is important to extend these observations on monocyte counts to other communities exposed to bone-seeking radionuclides, for example in uranium mining areas, areas near nuclear reprocessing plants and communities exposed to Chernobyl and weapon testing fallout. Persons exhibiting monocytopenia need to be medically observed until cellular immunity is restored since their ability to resist or survive diseases such as tuberculosis or meningitis appears to be impaired. In one community children with monocytopenia were treated with distilled water for drinking and cooking. They showed a marked increase in both monocyte and neutrophil counts within 6 months of beginning treatment.

Introduction

A normal healthy community has an average count of 0.35 to 0.40 ($\times 10^9$) monocytes per cubic millimetre of blood. Homeostatic controls maintain the count for the individual between 0.20 and 0.80 ($\times 10^9$) per cubic millimetre¹.

Monocytes are now thought to originate in bone marrow. Their transit time there is only 2.5 to 5 days. About four hundred million monocytes are delivered to the blood daily and about half migrate from the blood to tissue every 70 hours. The life span of monocytes in tissue is several months. Monocytes are able to divide outside of the bone marrow, have a phagocytic function, participate in delayed hypersensitivity and in viral immunity.

"The monocyte-macrophage may be regarded as a cellular mediator in the hemopoietic system, interacting with kinin, complement and clotting systems, and modulating production and destruction of red cells, granulocytes, lymphocytes and bone. It also influences the central nervous system through endotoxin-mediated pyrogens. The complexity of its func-

tions approaches that of the hepatocyte."²

It is also known that monocytes are required to process and present antigen to T and B lymphocytes, which in turn are stimulated to proliferate and differentiate into mature plasma cells that secrete specific antibodies. In particular, T lymphocytes mature into the helper/inducer T subsets and the suppressor cytotoxic T cells needed for effective immune response. A defect in any of these cell interactions results in alteration in immunoreactivity. While current research has focused on T and B lymphocyte response to radiation, there has been little research into monocyte response. Medical literature on hemotological response to radiation therapy and military radiobiological discussions deal with monocytopenia together with general reduction in number of all leukocytes. However these experiences are at relatively high dose levels.

In older texts the term "reticuloendothelial system" (RES) was used to describe the phagocytic system of the body thought to originate in the connective tissue. The more recent term for the phagocytic system is "monocyte-macrophage system" (MMS) reflecting the finding that the principal macrophage cells originate in bone marrow. This MMS has a capacity for rapid killing and destruction of bacteria and for "indefinite storage of particles such as silica, carbon and thorium dioxide."³

An increased monocyte count may indicate bacterial infection, protozoal infection, virus infection, malignant conditions, collagen diseases, chronic ulcerative colitis or regional enteritis. Monocytosis has been traditionally one of the diagnostic signs of tuberculosis. Some authors consider an absolute increase of monocytes to more than 0.50 ($\times 10^9$) per cubic millimetre as a monocytosis indicative of occult disease. Others use a cut off of 0.80 ($\times 10^9$) per cubic millimetre. The clinical significance of decreased monocyte count is unknown. However it has been observed in patients with disorders causing marrow replacement or marrow aplasia, and after radiation therapy or radiomimetic drugs.

Further insight into the role of monocytes comes from studies of the role of neuropeptides, produced by nerve cells in the brain, and their receptors. These neuropeptides include natural analogs of psychoactive drugs and even hormones, such as insulin, and the chemical substance angiotensin, which mediates thirst. According to researcher Candace B. Pert: "The new discovery I want to emphasize here is that every neuropeptide receptor that

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we have looked for is also on human monocytes.¹⁴ Absence or depletion of monocytes may have far reaching unexpected results on a human organism.

Case 1: McClure Crescent

A residential area within Scarborough, a suburb of Toronto, Canada, was contaminated with radium and its decay products. Contamination was about one-tenth as concentrated as one would expect to find in uranium mine tailings, but only two to three times higher than normal North American backyard soil. According to an engineering firm hired by the Canadian Atomic Energy Control Board, there was one "hot spot" where a radium source was buried, several pieces of property with other buried radioactive debris and other property either uncontaminated or having minor surface contamination. The government's estimate of radiation exposure to the average resident was 200 to 300 millirem (2 to 3 mSv) per year.

Fifty-eight children (15 years of age or under) were given three sequential complete blood counts (CBC) and differential testing in the course of a month. Thirty-six (62.1 percent) had at least one monocyte count less than 0.20 ($\times 10^9$) per cubic mm. All tests were conducted by the same laboratory, with one supervisor to assure uniformity. The children were examined for fever or sore throat, and eliminated if symptomatic. Age, sex and race were recorded for controlled analysis. Blood tests were all conducted by the MDS Laboratory, which had no knowledge of the exposure status of the residents.

Those children living on property identified by the engineering firm as having radioactive debris actually buried on it were classified as having high exposure. Those children living on property with no radioactive debris or only surface contamination were classified as low exposure. Children's high mobility in the neighbourhood argues against a "no exposure" category. Unfortunately the most popular spot for children to play in the neighbourhood was the backyard with the radioactive hot spot.

There were 34 children living on property with buried

radioactive debris and 24 with no detectable or only surface detectable debris.

The background line in Graph 1 shows an expected frequency distribution for monocyte counts in randomly selected normal population. No more than 5 percent of such a population would be expected to be below 0.20 ($\times 10^9$) and no more than 5 percent above 0.80 ($\times 10^9$) per cubic millimeter of blood due to chance. Stated in another way, 90 percent of a population would be expected to have a monocyte count between 0.20 and 0.80 ($\times 10^9$) per cubic millimetre of blood. Since our population was selected for good health, we expected less than 5 percent to have a monocyte count below 0.20 ($\times 10^9$) per cubic millimeter.

In contrast, 76.5 percent of the higher exposure children and 41.7 percent of the lower exposure children, had at least one clinically low count, below 0.20 ($\times 10^9$) per cubic millimetre of blood.

The tabulated results underlying Graph 1 are as follows:

	Higher Exposure	Lower Exposure
# of Children	34	24
# w/at least 1 low M count	26 (76.5%)	10 (41.7%)
# w/at least 2 low M counts	11 (32.4%)	2 (8.3%)
# w/3 low M counts	2 (5.9%)	None
# w/a zero M count	8 (23.5%)	None
Total # of observations	101	64
Observations w/low M count	39 (38.6%)	12 (18.8%)

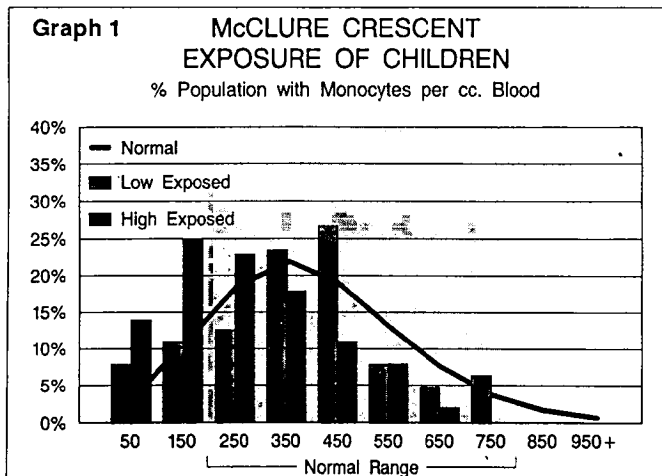
In addition, sixty-one adults were tested three consecutive times within a month's time. Each was screened for infectious disease. Age, sex and race were controlled in the analysis. The abnormal monocyte counts for those with higher and lower residential contamination against a background of normal are given in Graph 2.

A summary of the findings indicates:

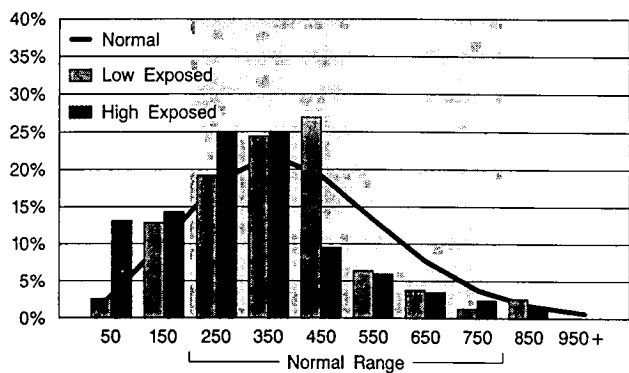
	Higher Exposure	Lower Exposure
# of Adults	30	31
# w/at least 1 low M count	16 (53.3%)	11 (35.5%)
# w/at least 2 low M counts	7 (23.3%)	1 (3.2%)
# w/3 low M counts	None	None
# w/a zero M count	2 (6.7%)	None
Total # of observations	84	78
Observations w/low M count	23 (27.4%)	12 (15.4%)

One child living on residential property with buried radioactive debris died of meningitis at age 16. He was 11 years old at the time of this study and had abnormal blood parameters. Unfortunately neither health authorities nor the family physician followed up on our findings and this child had no medical examination between age 11 and the terminal illness five years later.

One of the girls living in the home with the highest radiation exposure miscarried her first child about eight years after our testing. Her second child was Caesarean and she spent several weeks in intensive care after the



Graph 2 McCLURE CRESCENT
EXPOSURE OF ADULTS
% Population with Monocytes per cc. Blood



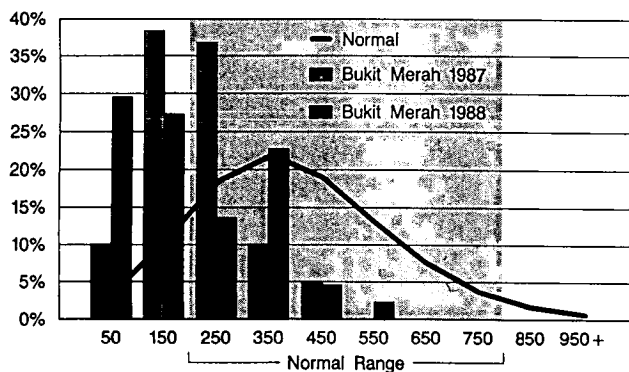
delivery with an intractable infection. She had had several blood tests showing monocytopenia when she was 12 years old. No follow up was done.

Case 2: Malaysian Children

Sixty children in 1987 and forty-four children in 1988, with suspected exposure to thorium hydroxide and lead sulfate waste from the Asian Rare Earth Company (A.R.E.) in Bukit Merah, Malaysia, were randomly selected and given CBCs with differential and blood lead testing. The CBCs were conducted in a uniform way by the Clinostic Laboratory in Ipoh, Malaysia and venous blood lead levels were done in a uniform way at Chemlab, in Selangor, Malaysia. There was one supervisor at each laboratory to assure the uniform quality of results.

The A.R.E. plant had been closed by court order in 1985 and ordered to construct a temporary storage building. Construction was completed and A.R.E. resumed operation in early 1987. The children tested in June 1987 were exposed to about 4 months of continuous plant operation. Those tested in June 1988 were exposed to about 16 months of continuous plant operation after resumption. In addition to its radioactive liquid and solid waste products, the plant emits two radioactive gases, radon and thoron. Monocyte counts for the 1987 and 1988 testing are presented as frequency distributions in Graph 3 against an

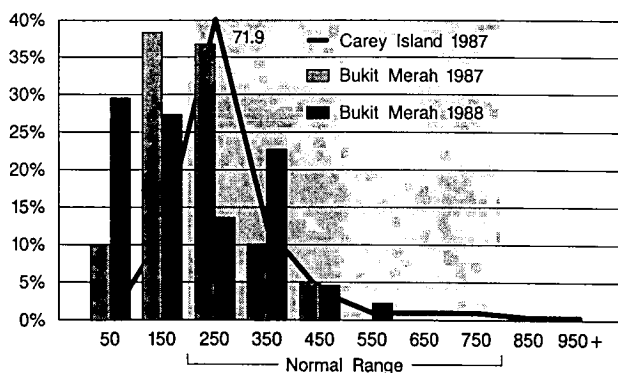
Graph 3 MALAYSIA
EXPOSURE OF CHILDREN
% Population with Monocytes per cc. Blood



expected normal background distribution.

There is an obvious shift toward lower monocyte counts with more prolonged exposure. In addition to the Bukit Merah children tested, 171 Malaysia children from Carey Island, a community of comparable socio-economic status, were tested. These children were found to have lower nutritional status than the Bukit Merah children but better health as measured by blood tests and physical examination. While 39 percent of the Bukit Merah children suffered from a triad of mild lymphadenopathy, congested turbinates and recurrent rhinitis, less than four percent of the Carey Island children presented with these problems. The Carey Island children were exposed to chemical effluence from a palm oil plant, pesticides and herbicides, but to our knowledge, not radioactive wastes. Monocyte counts for the Carey Island children relative to the Bukit Merah children are presented in Graph 4.

Graph 4 MALAYSIA
EXPOSURE OF CHILDREN
% Population with Monocytes per cc. Blood



Only children from Bukit Merah and Carey Island in a relatively healthy state, i.e. active, asymptomatic for infection and apparently normal, were included in the study. All medical testing was under the supervision of Dr. T. Jayabalan, a licensed Malaysian physician.

Findings with respect to the children's monocyte counts were as follows:

Characteristic	Carey Island		Bukit Merah	
	1987	1987	1987	1988
# of children	171	60	13	44
M < 0.10 ($\times 10^9$) per mm^3	0 (0%)	6 (10.0%)	13 (29.5%)	25 (56.8%)
M < 0.20 ($\times 10^9$) per mm^3	19 (11.1%)	29 (43.9%)	25 (56.8%)	25 (56.8%)
Average blood lead level	N.A.	12 $\mu\text{g}/\text{dl}$	12 $\mu\text{g}/\text{dl}$	27 $\mu\text{g}/\text{dl}$

Because of the possibility of lead toxicity being a marker for thorium exposure, since lead sulfate and thorium hydroxide wastes from A.R.E. are combined, Bukit Merah children whose parents worked in gasoline stations, or as plumbers, battery workers or paint factory workers, had been excluded from the monocyte study. Malaysia had also mandated the use of unleaded gas for automobiles. Hence we believe that the increased lead levels in blood

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in 1988 are attributable to the A.R.E. plant.

Since the lead sulfate waste reached the children, we assumed the thorium hydroxide waste also reached them. Thorium is a radioactive heavy metal which humans store in bone.

Lead is known to affect white blood count, and we were not sure whether or not it would affect monocytes.

Parents whose children had depressed monocytes in the 1987 testing were advised to send them away from Bukit Merah on weekends and school holidays. In the 1988 testing there were 33 "new" children, i.e. they were not tested in 1987. These children were not advised to spend time away from Bukit Merah, although some parents may have adopted this as precautionary measure because of their neighbours. This may account for the bimodal nature of the Bukit Merah 1988 frequency function.

A follow-up of the Malaysian children was undertaken. It became apparent in early 1989 that the community around the A.R.E. plant was experiencing even more severe haematological problems. Two children, ages five and 11, were diagnosed with acute leukemia, both born in Bukit Merah. A 19-year-old man, born in Bukit Merah and a life-long resident was also diagnosed with acute leukemia. This young man worked in a cottage industry located near the plant. A two-year-old child living within the 10km radius of the plant died of septicemia and a 22-year-old A.R.E. worker died with a diagnosis of meningoencephalitis. In neither of the last two cases was a bone marrow test undertaken. On admission to the hospital, the worker's blood count was abnormally low in view of his overwhelming infection, 6.60×10^9 white cells per cubic millimetre of blood. His monocyte count is not known. Another child of about five years old developed a brain cancer.

According to the official 1986 Malaysian statistics, leukemia of all types and for all ages occurs at a rate of 0.83 per 10^5 persons per year in peninsular Malaysia. About 23 percent are in those under 20 years of age, giving a rate of about 0.19 per 10^5 persons. For Bukit Merah, with a population of approximately 15,000, one would expect 0.03 cases a year. This means a case roughly every 30 years. Three cases diagnosed within six months is highly significant with the probability that it happened by chance equal to 0.00003 (3 chances in 100,000).

Case 3: Rongelap Control Population

After a nuclear test of a 15 megaton hydrogen bomb at Bikini Atoll in March 1, 1954, there was serious nuclear fallout on Rongelap Atoll, an inhabited downwind group of islands. With U.S. Congressional funding, the Brookhaven National Laboratory on Long Island undertook medical follow-up of those Rongelap people who were on the atoll at the time of the fallout. Brookhaven scientists also chose an age-matched group of Rongelapese not on the atoll at the time of the fallout to use as a comparison population.

This second group is called the "unexposed" control population. Their exposure to the nuclear fallout was undoubtedly less than that of the group on Rongelap Atoll at the time of the fallout. However, it has never been established that this population had "no exposure" to the fallout since obviously there was some residual contamination on the atoll where they lived from 1957 on.

There were 134 people in the "unexposed" control group, who returned to the contaminated Rongelap Atoll in 1957 with the returning "exposed" Rongelapese. The yearly CBC and differentials for "unexposed" (five tests each) for 1957 to 1966 were released by Brookhaven to IICPH in February 1988. Brookhaven has refused to release the blood test results for the "exposed" population.

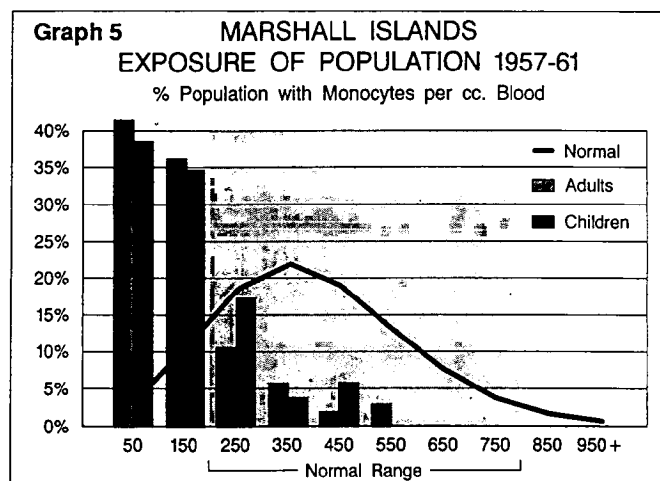
The average monocyte count for this control population was 0.169×10^9 per cubic millimetre, below the 0.20×10^9 per cubic millimetre considered the lower limit of normal. By 1962 to 1966, the number of "unexposed" living on Rongelap had increased to 158, and their average monocyte count increased to 0.20×10^9 per cubic millimetre, meaning a substantial fraction were still below normal. All laboratory tests were conducted by the Brookhaven National Laboratory (BNL).

In 1982-1986, 69 "unexposed" persons were living on the Atoll, and their monocyte count average, according to BNL, had risen to 0.328×10^9 per cubic millimetre.

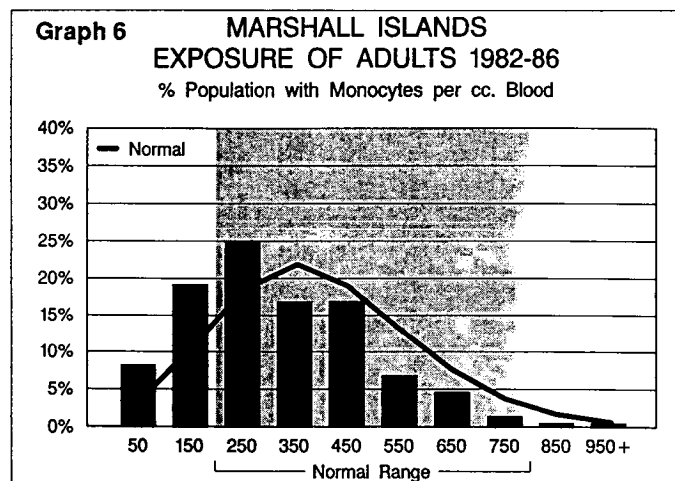
There is no reason to believe the Rongelap people have abnormal monocyte counts due to heredity. They are Micronesians, believed to have originated in Asia. Micronesians and Asians generally have the same blood count normals as Caucasians.

Because of weathering which reduced contamination of the atoll, and increased reliance on food imported from North America, residual nuclear radiation exposure to the Rongelapese has gradually declined since 1957. This is the presumed explanation of the return to more normal monocyte counts in the 1982-1986 period.

Out of 76 "unexposed" Rongelapese tested between 1957 and 1961, sixty (78.9 percent) had one or more monocyte counts below 0.20×10^9 per cubic millimetre of blood. In 1982-1986, fifty (57.0 percent) out of eighty-nine "unexposed" had counts below 0.20×10^9 per cubic



millimetre. In the 1957–1961 period twenty (26.3 percent) had at least one zero monocyte count, and in the 1982–1986 period eight (9.0 percent) had at least one zero monocyte count. Graph 5 gives the frequency distributions for monocyte counts of Rongelapese children and adults in the 1957–1961 period.



The Brookhaven research team added to the “unexposed” control population over the years as some Rongelapese were lost to follow up. The Brookhaven “unexposed,” all adults in 1982–86, had a more normal monocyte distribution.

We found fifty-eight persons with medical records in both the 1957–61 and 1982–86 time periods, with one or more low monocyte counts in the early period and no other blood abnormality. Of these 58 Rongelapese with monocytopenia in 1957–61, we found in 1982–1986:

- 8 (13.7 percent) had normal blood parameters
- 39 (67.2 percent) still had monocytopenia
- 8 (13.8 percent) had monocytosis
- 3 (5.2 percent) had normal monocyte counts but other abnormal blood parameters

The same 58 individuals who had normal blood counts except for monocytopenia in 1957–61, were examined for subsequent neutropenia and lymphopenia.

In 1982–1986 we found:

- 7 (12.1 percent) with neutropenia
- 4 (6.9 percent) with lymphopenia
- 3 (5.2 percent) with both neutropenia and lymphopenia

One of the individuals had a total white count of 1.80 ($\times 10^9$) cells per cubic millimetre (0.31 N, 1.39 L, 0 M, and 0.50 E).

Case 4:

A North American Indian band, the Mississauga First Nation, living on the north shore of Lake Huron, had been exposed to uranium dust from a June 1990 accident at the CAMECO uranium refinery. Within the first six months after the accident monocyte counts were depressed for all age groups. The adults were able to restore normal mono-

Table 1
Blood Test Results for Children Under Seven Years

Blood parameter	1/92	4/92	9/92	12/92
Erythro ($\times 10^{12}$)	4.50	4.73	4.56	4.56
Hemo	127	132	131	130
Hema	0.372	0.394	0.41	0.375
MCV	82.2	83.4	88.9	81.8
MCH	28.2	28.0	28.8	28.5
MCHC	343	336	324	347
Leuko ($\times 10^9$)	8.03	7.62	8.43	8.61
Neutro ($\times 10^9$)	3.60	4.06	4.38	4.51
Lympho ($\times 10^9$)	3.67	2.96	3.18	3.05
Mono ($\times 10^9$)	0.38	0.27	0.33	0.69
Eosin ($\times 10^9$)	0.38	0.31	0.45	0.29
Baso ($\times 10^9$)	0.04	0.03	0.08	0.05

Study Variables (Number)

Monocytopenia	5	5	4	—
Probable anemia	4	1	—	—

Other (Number)

Leukopenia	1	—	—	1
Lymphopenia	—	3	3	3
Neutropenia	2	2	2	1
Eosinophilia	3	1	3	2
Atypical lymphs	6	1	—	—

cyte counts in about a year. However the children between ages three and seven persisted with monocytopenia for more than two years after the accident.

These children often had an accompanying iron deficient anemia and neutropenia as well as monocytopenia. Table 1 shows the complete blood count average taken four times during 1992.

Most children were on a regime of distilled water for drinking and cooking by September 1992. In addition to the recovery of monocyte count there was an increase in neutrophil count and a decrease in iron deficient anemia. Table 2 (page 26) shows the children’s average monocyte counts from the time of the accident, June 1990, to December 1992.

It is thought that distilled water leaches inorganic heavy metals, including uranium, from the body. Distilled water used in cooking would also help to remove heavy metal from food. The distilled water replaced the Reserve drinking water which has higher than normal uranium levels.

Further Research Needed

Sensitive immunological testing of children with monocytopenia is needed to elucidate the biological mechanism of cellular immune depression with low dose radiation exposure. Implications of monocytopenia for diseases involving neuro-transmitters may also prove important.

Monocytopenia in other radiation exposure populations,

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Table 2

Average Monocyte Counts for Children Under Seven Years

Testing	Average Monocyte Count (x10 ⁹)
Norm	0.30 to 0.75*
June 1990	0.25
August 1990	0.29
January 1991	0.32
January 1992**	0.37
April 1992	0.27
September 1992	0.33
December 1992	0.69

* *Textbook of Haematology*, R.B. Thompson and S.J. Proctor and Neilson's *Pediatric Textbook*

** Beginning of HIP program

especially those exposed to particulate bone-seeking radionuclides, should be examined. Distilled water as a treatment, with substitution of fruit juices after strenuous

exercise or play, needs to be tried in other populations and in controlled clinical trials.

Acknowledgements

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- 1 Eastham, R.D. *Clinical Haematology*, Bristol, 1986.
- 2 *Ibid.* p. 249
- 3 *Haematology*, edited by William S. Bede, MIT Press 1985, p.27
- 4 Candace B. Pert: "The Wisdom of the Receptors: Neuropeptides, the Emotions and Bodymind," *ADVANCES*, Institute for the Advancement of Health Vol. 3, No.3, 1986, pp. 8-16.

